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EXAMINER

SCHUBERG, LAURA J

ART UNIT	PAPER NUMBER
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1651

DATE MAILED: 05/30/2006

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No. 10/681,753	Applicant(s) WILLIAMS ET AL.	
	Examiner Laura Schuberg	Art Unit 1651	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

- 1) ☒ Responsive to communication(s) filed on 16 March 2006.
- 2a) ☐ This action is **FINAL**. 2b) ☒ This action is non-final.
- 3) ☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

- 4) ☒ Claim(s) 1,3-22,24-31 and 35-38 is/are pending in the application.
- 4a) Of the above claim(s) _____ is/are withdrawn from consideration.
- 5) ☐ Claim(s) _____ is/are allowed.
- 6) ☒ Claim(s) 1,3-22,24-31,35-38 is/are rejected.
- 7) ☐ Claim(s) _____ is/are objected to.
- 8) ☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

- 9) ☐ The specification is objected to by the Examiner.
- 10) ☐ The drawing(s) filed on _____ is/are: a) ☐ accepted or b) ☐ objected to by the Examiner.
 Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).
 Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).
- 11) ☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

- 12) ☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).
- a) ☐ All b) ☐ Some * c) ☐ None of:
1. ☐ Certified copies of the priority documents have been received.
2. ☐ Certified copies of the priority documents have been received in Application No. _____.
3. ☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).
- * See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

- | | |
|--|---|
| 1) ☒ Notice of References Cited (PTO-892) | 4) ☐ Interview Summary (PTO-413)
Paper No(s)/Mail Date. _____ |
| 2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948) | 5) ☐ Notice of Informal Patent Application (PTO-152) |
| 3) ☒ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08)
Paper No(s)/Mail Date <u>12/30/03 5/3/06</u> | 6) ☐ Other: _____ |

DETAILED ACTION

Election/Restrictions

Applicant's specie election of growth factor in the reply filed on 03/16/2006 is acknowledged. Because applicant did not distinctly and specifically point out the supposed errors in the restriction requirement, the election has been treated as an election without traverse (MPEP § 818.03(a)).

Claim Rejections - 35 USC § 112

The following is a quotation of the second paragraph of 35 U.S.C. 112:

The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

Claims 1,13, and 19 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

Regarding claims 1,13, and 19, the term "optionally" renders the claim indefinite because it is unclear whether the limitation(s) following the term are part of the claimed invention. See MPEP § 2173.05(d).

Claim 21 is rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

The term "Irgacure 2959" is a trade name for a particular photoinitiator.

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According to the MPEP 2173.05, the use of a trademark or trade name in a claim to identify or describe a material or product would not only render a claim indefinite, but would also constitute an improper use of the trademark or trade name. Appropriate correction is required.

Claim Rejections - 35 USC § 102

The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

A person shall be entitled to a patent unless –

(b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.

(e) the invention was described in (1) an application for patent, published under section 122(b), by another filed in the United States before the invention by the applicant for patent or (2) a patent granted on an application for patent by another filed in the United States before the invention by the applicant for patent, except that an international application filed under the treaty defined in section 351(a) shall have the effects for purposes of this subsection of an application filed in the United States only if the international application designated the United States and was published under Article 21(2) of such treaty in the English language.

Claims 1,3,4,6,24,36 are rejected under 35 U.S.C. 102(b) as being anticipated by Dunn et al (Biotechnol. Prog. 1991).

Claim 1 is drawn to a method of producing a multi-layered tissue construct comprising the steps of:
providing a first polymerizable mixture, including, optionally, a first polymerization initiator; providing a second polymerizable mixture, including, optionally, a second polymerization initiator; wherein one of the first and second mixtures comprises cells; placing a volume of the first mixture in a space, then crosslinking the first mixture for a

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first predetermined time until the first mixture forms an at least partially gelled first layer; and placing a volume of the second mixture in the space with the at least partially gelled first layer, then crosslinking the second mixture for a second predetermined time until the second mixture is at least partially gelled to form a second layer.

Claim 3 is drawn to the method according to claim 1, further comprising the step of adding a suspension of cells to a surface of the at least partially gelled first layer, before the step of placing the volume of the second mixture in the space.

Claim 4 is drawn to the method according to claim 1, wherein one of the first bioactive substance selected from the group consisting of: a nutrient, a cellular mediator, a growth factor, a compound which induces cellular differentiation, a bioactive polymer, a gene vector, or a pharmaceutical. (Applicant elected growth factor)

Claim 6 is drawn to the method as recited in claim 5, further comprising the step of: additionally crosslinking the first mixture and the second mixture until the first layer and the second layer further polymerize to form an integrated multi-layered gel.

Claim 24 is drawn to a multi-layered tissue construct comprising:
a first layer comprising a first hydrogel; and a second layer comprising a second hydrogel, wherein the first layer is connected to the second layer at a first transition zone and wherein at least one of the first layer and the second layer further comprises cells.

Claim 36 is drawn to the multi-layered tissue construct as recited in claim 24, wherein the first layer comprises a bioactive substance selected from the group consisting of: a nutrient, a cellular mediator, a growth factor, a compound which induces

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cellular differentiation, a bioactive polymer, a gene vector, or a pharmaceutical.

(Applicant elected growth factor)

Dunn teaches a method for culturing hepatocytes that includes adding a suspension of cells to an at least partially gelled first layer of collagen before adding a collagen solution on top of the first layer and then allowing the culture to gel and crosslink for attachment of the two layers before adding media (p.238 col1-2). In addition, media containing cells and growth factor are added to the first layer before the second layer is added (p.238).

Therefore, Dunn explicitly teaches all the limitations of Applicant's claimed invention.

Claims 1,4,24,25,35-38 are rejected under 35 U.S.C. 102(b) as being anticipated by Dionne et al (US 5,798,113).

Claims 1,4,24,36 are drawn to the method and construct as described above.

Claim 25 is drawn to the multi-layered tissue construct as recited in claim 24, wherein the first layer comprises cells of a first cellular type encapsulated in the first hydrogel.

Claim 35 is drawn to the multi-layered tissue construct as recited in claim 25, wherein the first layer further comprises cells of a second cellular type encapsulated in the first hydrogel.

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Claim 37 is drawn to the multi-layered tissue construct as recited in claim 25, wherein the first layer also includes a bioactive substance.

Claim 38 is drawn to the multi-layered tissue construct as recited in claim 25, wherein the second layer includes a bioactive substance.

Dionne teaches a method of making a dual-matrix vehicle which includes mixing a suspension of pancreatic islet cells in an alginate solution, crosslinking the mixture with a CaCl_2 bath for a predetermined time, adding a second mixture of alginate to form a second layer and crosslinking again with a CaCl_2 bath (column 30 example 3). The CaCl_2 bath acts as a polymerization initiator. The addition of growth factors to the first layer is taught (column 9 line 55) as well as bioactive substances to the second layer (column 13 line 43-55). The addition of a second cell type encapsulated in the first hydrogel along with the first cell type is also taught (column 10 line 5-14).

Therefore, Dionne explicitly teaches all the limitations of Applicant's claimed invention.

Claims 1,4-10, 12-19, 24-28, 30, 35-38 are rejected under 35 U.S.C. 102(e) as being anticipated by Sah et al (US 2003/0077821 A1).

Claims 1,4,24,25,35-38 are drawn to the method and construct as described above.

Claim 5 is drawn to the method as recited in claim 1, wherein the step of providing the first mixture includes mixing the first polymerizable mixture with first cells to form a first polymer-cell suspension, and the step of providing the second mixture

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includes mixing the second polymerizable mixture with second cells to form a second polymer-cell suspension.

Claim 6 is drawn to the method as recited in claim 5, further comprising the step of: additionally crosslinking the first mixture and the second mixture until the first layer and the second layer further polymerize to form an integrated multi-layered gel.

Claim 7 is drawn to the method as recited in claim 5, wherein the first cells and the second cells are selected from the group of cell types consisting of superficial zone chondrocytes, middle zone chondrocytes, and deep zone chondrocytes.

Claim 8 is drawn to the method as recited in claim 7, wherein the first cells are a cell type different from the second cells.

Claim 9 is drawn to the method as recited in claim 8, wherein the first cells are deep zone chondrocytes and the second cells are superficial zone chondrocytes.

Claim 10 is drawn to the method as recited in claim 7, further comprising the step of: harvesting mammalian articular cartilage and excising tissue specimens corresponding to an upper zone, a middle zone and a deep zone of the cartilage; and separately digesting the tissue specimens from the upper zone, the middle zone and the deep zone respectively to isolate upper zone chondrocytes, middle zone chondrocytes and deep zone chondrocytes.

Claim 12 is drawn to the method as recited in claim 6, further comprising the step of incubating the multi-layered gel in a complete media for a predetermined incubation period to form the multi-layered tissue construct.

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Claim 13 is drawn to the method as recited in claim 5, further comprising the steps of: providing a third polymerizable mixture, including, optionally, a third polymerization initiator, wherein the third polymerizable mixture is mixed with third cells to prepare a third polymer-cell suspension; and placing a volume of the third mixture in the space with the at least partially gelled first layer and the at least partially gelled second layer, then crosslinking the third mixture for a third predetermined time until the third mixture is at least partially gelled to form a third layer.

Claim 14 is drawn to the method as recited in claim 13, further comprising the step of: additionally crosslinking the first layer, the second layer and the third layer to form an integrated multi-layered gel.

Claim 15 is drawn to the method as recited in claim 14, wherein the first cells, the second cells, and the third cells are selected from the group of cell types consisting of superficial zone chondrocytes, middle zone chondrocytes, and deep zone chondrocytes.

Claim 16 is drawn to the method as recited in claim 15, wherein the first cells, the second cells and the third cells are selected to be different cell types.

Claim 17 is drawn to the method as recited in claim 15, wherein the first cells are deep zone chondrocytes, the second cells are middle zone chondrocytes, and the third cells are superficial zone chondrocytes.

Claim 18 is drawn to the method as recited in claim 17, further comprising the step of: incubating the multi-layered gel in a complete media for a predetermined incubation period to form the multi-layered tissue construct.

Claim 19 is drawn to the method as recited in claim 13, further comprising the steps of: additionally crosslinking the first layer, the second layer and the third layer until the first layer, the second layer and the third layer completely polymerize to form a multi-layered gel; and **optionally** incubating the multi-layered gel in a complete media for a predetermined period of time to form the multi-layered tissue construct.

Claim 26 is drawn to the multi-layered tissue construct as recited in claim 25, wherein the second layer comprises cells of a second cellular type encapsulated in the second hydrogel, and the first cell type is different from the second cell type.

Claim 27 is drawn to the multi-layered tissue construct as recited in claim 26, further comprising: a third layer comprising cells of a third cellular type encapsulated in a third hydrogel, wherein a second transition zone connects the third layer to the second layer, and the third cell type is different from the second cell type.

Claim 28 is drawn to the multi-layered tissue construct as recited in claim 27, wherein the first cell type is a deep zone chondrocyte, the second cell type is a middle zone chondrocyte, and the third cell type is a superficial zone chondrocyte.

Claim 30 is drawn to the multi-layered tissue construct as recited in claim 26, wherein the first cell type is a deep zone chondrocyte and the second cell type is a superficial zone chondrocyte.

Sah teaches a tissue-engineered, cohesive cartilage construct comprised of two or more cartilage layers, wherein each cartilage layer comprises chondrogenic cells having a chondrocytic phenotype corresponding to superficial zone, middle zone, and deep zone chondrocytes (p.3 para 28). The polymerizable mixture taught by the

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reference is the cells and their associated matrix which form a hydrogel after a period of time in culture (p.9 para 82). Additional layers are not added until the current layer coalesces (p.9 para 82). Each layer of cells is taught to include the addition of growth factors (bioactive substances) (p.7 para 58) as well. The steps of providing the first and second polymerizable mixtures includes mixing agarose or sodium alginate with the cells to produce the cell associated matrix necessary to form the hydrogels for each layer (p.5 para 48). The crosslinks are taught to increase over time (p.7 para 59) and since the multi-layered constructs were cultured for 1 or 2 weeks with daily changes of complete medium (p.9 para 82) it is inherent that the layers further polymerize to form an integrated multi-layered gel. The reference also teaches that the construct is not limited in the order of the layers of chondrocytes and that superficial zone chondrocytes can be adjacent to a layer containing deep zone chondrocytes (p.3 para 31). The order of layers found in natural cartilage is preferred and taught to be the first cells are deep zone chondrocytes, second cells are middle, and third cells are superficial (p.3 para 30). In addition, the steps of harvesting mammalian articular cartilage, excising tissue corresponding to the upper, middle and deep zone of the cartilage, and digesting the specimens from the different zones to isolate the different zone chondrocytes are also taught by the reference (p.5 para 41-45). The first layer of the construct may also contain a second cellular type encapsulated in the first hydrogel (p.3 para 29).

Therefore, Sah teaches all the limitations of Applicant's claimed invention.

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Claims 1, 4-6, 8, 11-14, 16, 19, 24-27, 35-38 are rejected under 35 U.S.C. 102(e) as being anticipated by Mizuno et al (US 6,949,252 B2).

Claims 1, 4-6, 8, 12-14, 16, 19, 24-27, 35-38 are drawn to the method and construct as described above.

Claim 11 is drawn to the method as recited in claim 5, wherein the cell concentration of each suspension is approximately 20 million cells/cc.

Mizuno teaches compositions and methods for preparing tissues and tissue constructs which include multi-layered systems comprising at least two layers (column 9 line 67). Cells are present in at least one layer of the construct but may be also be present in three layers and may include three cell types (column 22 line 10- 32). The cellular layers are formed from a polymerizable mixture that forms a hydrogel by crosslinking (column 11 line 50- column 12 line 8). The addition of growth factors to the first and second layer is taught (column 10 line 5) as well as a cell concentration of **approximately** 20 million cells/cc (column 16 line 63). Incubating the multi-layered gel in a complete medium to form the multi-layered tissue construct is also taught (column 15 line 20-47).

Therefore, Mizuno teaches all the limitations of Applicant's claimed invention.

Claim Rejections - 35 USC § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

(a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the

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invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negated by the manner in which the invention was made.

The factual inquiries set forth in *Graham v. John Deere Co.*, 383 U.S. 1, 148

USPQ 459 (1966), that are applied for establishing a background for determining

obviousness under 35 U.S.C. 103(a) are summarized as follows:

1. Determining the scope and contents of the prior art.
2. Ascertaining the differences between the prior art and the claims at issue.
3. Resolving the level of ordinary skill in the pertinent art.
4. Considering objective evidence present in the application indicating obviousness or nonobviousness.

Claims 1, 4-6, 8, 11-14, 16, 19-22, 24-27, 35-38 are rejected under 35 U.S.C.

103(a) as being unpatentable over Mizuno et al (US 6,949,252 B2) in view of Desai et al (US 5,550,178).

Claims 1, 4-6, 8, 11-14, 16, 19, 24-27, 35-38 are drawn to the method and construct as described above.

Claim 20 is drawn to the method as recited in claim 5, wherein the first polymerizable mixture and the second polymerizable mixture both include photopolymerizable poly(ethylene glycol) diacrylate dissolved in solvent, which is phosphate buffered saline, to make a 10% w/v solution, and the first polymerization initiator is added to the first mixture and the second polymerization initiator is added to the second mixture, wherein both the first polymerization initiator and the second polymerization initiator are the same photoinitiator, and each suspension has a concentration of 20 million cells/cc.

Claim 21 is drawn to the method as recited in claim 20, wherein the photoinitiator is Irgacure 2959 mixed to a concentration of 0.05% w/v in each suspension.

Claim 22 is drawn to the method as recited in claim 21, wherein crosslinking of the first polymerizable mixture is controlled by exposure to external radiation and crosslinking of the second polymerizable mixture is controlled by exposure to the external radiation.

Mizuno teaches the method and composition of claims 1, 4-6, 8, 11-14, 16, 19, 24-27, 35-38 as described above. Mizuno teaches using ultraviolet radiation to crosslink the polymerizable mixture (column 12 line 6).

Mizuno does not specifically teach the photopolymerizable poly (ethylene glycol) diacrylate or the photoinitiator Irgacure 2959.

Desai teaches a method for encapsulating cells (column 4) and includes 10% w/v poly (ethylene glycol) diacrylate in phosphate buffered saline and a photoinitiator (column 11-12) as suitable for crosslinking.

Langer teaches compositions for tissue engineering using photocrosslinkable polymeric hydrogels and photoinitiators at a concentration of 0.05% w/v (column 15) with poly (ethylene glycol) diacrylate (column 5).

Domschke teaches the use of hydrogels for implants (p.1 para 2) and suggests the use Irgacure 2959 at 0.05 % by weight (p.3 para 25-26).

One of ordinary skill in the art would have been motivated to include the 10% w/v poly (ethylene glycol) diacrylate in phosphate buffered saline and a photoinitiator in the method of Mizuno because Desai teaches that they are suitable for polymerizing

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encapsulated cells (col 11-12) and Mizuno suggests the use of chemicals and radiation for solidifying the cellular support matrix (column 12). One of ordinary skill in the art would have had a reasonable expectation of success because Desai was teaching the use of these chemicals for encapsulation of cells as well (column 4).

One of ordinary skill in the art would have been motivated to use Irgacure 2959 at a concentration of 0.05% because Domschke teaches that this is a suitable photoinitiator for hydrogels for implants (p.3) and Mizuno teaches using ultraviolet radiation to crosslink the polymerizable mixture (column 12 line 6). One of ordinary skill in the art would have had a reasonable expectation of success since Mizuno, Langer and Domschke are all teaching methods using hydrogels for tissue engineering and photopolymerization.

Claims 1,4-19, 24-31, 35-38 are rejected under 35 U.S.C. 103(a) as being unpatentable over Sah et al (US 2003/0077821 A1) in view of Desai et al (US 5,550,178).

Claims 1,4-19, 24-28, 30, 35-38 are drawn to the method and composition as described above.

Claim 29 is drawn to the multi-layered tissue construct as recited in claim 28, wherein the first hydrogel, the second hydrogel and the third hydrogel include photopolymerized poly(ethylene glycol) diacrylate.

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Claim 31 is drawn to the multi-layered tissue construct as recited in claim 30, wherein the first hydrogel and the second hydrogel both include photopolymerized poly(ethylene glycol) diacrylate.

Sah teaches the method and composition of claims 1,4-10, 12-19, 24-28, 30, 35-38 as described above.

Sah does not teach using photopolymerized poly(ethylene glycol) diacrylate or that the number of cells seeded is 20 million/cc.

Langer teaches compositions for tissue engineering using photocrosslinkable polymeric hydrogels with poly (ethylene glycol) diacrylate (column 5). Langer also teaches that the number of cells suspended in the polymer is most preferably between 10 and 20 million cells/ml (column 10).

One of ordinary skill in the art would have been motivated to use the photopolymerized poly(ethylene glycol) diacrylate in the composition of Sah because Langer teaches that this is an alternative to forming hydrogels and suggests collagen as a suitable polymer (column 4) which is the polymer that Sah uses. One of ordinary skill in the art would have been motivated to seed 10-20 million cells/cc into the suspension of Sah because Langer teaches that this is a suitable number of cells for implantation. One would have been motivated to seed closer to 20 million cells in case all cells were not viable and some were lost in the process. One of ordinary skill in the art would have had a reasonable expectation of success because both Sah and Langer (column 9) are teaching methods of implanting chondrocytes.

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Conclusion

No claims are allowed.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Laura Schuberg whose telephone number is 571-272-3347. The examiner can normally be reached on Mon-Fri 8:00-4:30.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Michael Wityshyn can be reached on 571-272-0926. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see <http://pair-direct.uspto.gov>. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

Laura Schuberg

SANDRA E. SAUCIER
PRIMARY EXAMINER

